

## LETTERS TO THE EDITOR

# Additional antiretroviral and immunosuppressive drug-drug interactions

**To the Editor:** As appropriately pointed out in the review article by Izzedine et al [1], cyclosporine, tacrolimus, and sirolimus share the same metabolic pathways (CYP450 3A4 isoenzyme) as all of the protease inhibitors (PI) used in treatment of human immunodeficiency virus (HIV). However, Table 1 lacks current information regarding other PIs. Atazanavir sulfate (Reyataz®), FDA approved in June 2003, competitively inhibits CYP3A4, CYP1A2, CYP2C9, uridine diphosphate-glucuronosyl transferase (UGT) 1A1 enzyme, and P-glycoprotein (P-gp) at doses used in current clinical practice [2, 3]. Although no pharmacokinetic studies have been completed with the above immunosuppressants, it would be reasonable to assume that atazanavir would cause increases in their plasma levels.

In addition, tipranavir, another PI, is now available through an expanded access program with Boehringer Ingelheim while it awaits FDA approval. Unlike other PIs, tipranavir is an inducer on CYP3A4, thus potentially decreasing the levels of these immunosuppressants. However, the induction of CYP3A4 by tipranavir is lost when pharmacologically boosted with ritonavir [4]. With the addition of these two PIs to the market, I felt that it was important for the readers to also consider this information.

Lastly, Table 1 indicates that enfuvirtide (T-20) and tenofovir (TFV) are PIs. This is incorrect because T-20 is classified as a fusion inhibitor, and tenofovir a nucleotide reverse transcriptase inhibitor. Due to similar mechanisms of action, tenofovir (a nucleotide reverse transcriptase inhibitor) is commonly categorized with the standard nucleoside reverse transcriptase inhibitors (NRTI). Based on the pharmacokinetic profiles of T-20 and tenofovir, no drug interactions are expected with the immunosuppressants reviewed.

ANTHONY J. BUSTI  
Dallas, Texas

Correspondence to Anthony J. Busti, Department of Pharmacy Practice, Texas Tech University Health Sciences Center, School of Pharmacy Dallas Fort Worth Regional Campus, 4500 S. Lancaster Rd., Bldg. 7, Rt-119A, Dallas, TX 75216.  
E-mail: [Anthony.busti@ttuhsc.edu](mailto:Anthony.busti@ttuhsc.edu)

## REFERENCES

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## Reply from the Authors

We thank Dr. Busti for his interesting comments on our article [1]. The reason why we decided not to include atazanavir and tipranavir in our review is that they were either not available, or very recently released at the time we wrote this article. We thus thought that more clinical experience was needed before adding those drugs to such a review. However, Dr. Busti comments well complete our article, and we agree with his conclusions.

We totally agree that tenofovir and enfuvirtide have been misclassified in tables. This obviously results from an editing error.

Finally, we would not be as confident as Dr. Busti on the lack of interactions between immunosuppressive and tenofovir or enfuvirtide. Indeed, interactions through drug transporters in the kidney, the liver, and/or the intestine are frequent, and because tenofovir interactions with such transporters have been studied, some other pathways are still under investigation, as well as for enfuvirtide.

HASSANE IZZEDINE, VINCENT LAUNAY-VACHER,  
ALAIN BAUMELOU, and GILBERT DERAY  
Paris, France

Correspondence to Hassane Izzedine, Department of Nephrology, Pitié-Salpêtrière Hospital, Paris, France.  
E-mail: [hassan.izzedine@psl.ap-hop-paris.fr](mailto:hassan.izzedine@psl.ap-hop-paris.fr)

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1. IZZEDINE H, LAUNAY-VACHER V, BAUMELOU A, DERAY G: Antiretroviral and immunosuppressive drug-drug interactions: An update. *Kidney Int* 66:532–541, 2004